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Glyburide Disposition During Pregnancy

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1. Introduction

During pregnancy, 5-14% of women are diagnosed with gestational diabetes mellitus (GDM) and the incidence has been increasing (Jovanovic & Pettitt, 2001; Paglia & Coustan, 2011). While insulin treatment is still the "gold standard" therapy for controlling maternal glycemia, the increasing use of oral anti-diabetic agents such as glyburide and metformin has begun to change standard care (Maymone et al., 2011). Anti-diabetic drugs are often titrated over a prolonged period of time to achieve glycemic control. Prolonged hyperglycemia increases the likelihood of adverse fetal/neonatal and maternal outcomes. Thus, quickly achieving glycemic control during pregnancy can significantly reduce the occurrence of certain adverse perinatal and maternal outcomes (Karakash & Einstein, 2011).
Glyburide is a second generation oral sulfonylurea (Feldman, 1985). Glyburide lowers blood sugar levels by stimulating the pancreas to secrete insulin and by helping the body use insulin efficiently. Considerable data in the literature suggest that glyburide may be a safe alternative to insulin for the treatment of GDM due to its similar efficacy to insulin and its low fetal distribution (Nicholson & Baptiste-Roberts, 2011; Maymone et al., 2011). Physiological and biochemical changes that occur during pregnancy alter the pharmacokinetics of glyburide, thus affecting the safety and efficacy of the drug for both the mother and the fetus. Understanding pregnancy-induced changes in the disposition of glyburide (including fetal exposure) will be important for optimizing dosage guidelines during pregnancy. In this chapter, current knowledge on the safety and efficacy of glyburide for the treatment of GDM, pregnancy-related effects on maternal disposition as well as placental transport and metabolism of the drug will be summarized.

2. Gestational diabetes mellitus and treatment options

The American College of Obstetricians and Gynecologists (ACOG) committee on practice defines GDM as "carbohydrate intolerance that begins or is first recognized during pregnancy" (2001). Similar to type II diabetes mellitus, GDM is the result of an inability to compensate for the degree of insulin resistance. Insulin resistance is normal to some extent during pregnancy as a means of ensuring that glucose is freely available to the developing fetus; however, in women predisposed to diabetes, the degree of insulin resistance can be so high that treatment is necessary to maintain euglycemia.

Properly treating GDM is of great concern as the condition complicates 5-14% of pregnancies. If untreated, GDM presents a danger to both the mother and baby, particularly the risk of hypertension, preeclampsia, urinary tract infections, cesarean delivery and development of type II diabetes mellitus later in life in mothers, as well as macrosomia, neonatal hypoglycemia, childhood obesity and type II diabetes mellitus in the offspring (2002; 2009; 2010; Paglia & Coustan, 2011). Diet therapy is the first line of treatment for GDM and is adequate for controlling glucose concentrations in the majority of patients. Those failing diet therapy are managed with the addition of pharmacotherapy (Landon et al., 2007). The American Diabetes Association (ADA) suggests that women with GDM should seek nutritional counseling by a dietician in order to individualize diet therapy by patient height and weight (2001). To prevent ketonuria, which can hinder the cognitive development of children ages 3 – 9, the ACOG recommends caloric restrictions that are not to exceed 33% of current diet (2001).

There are two general options of pharmacotherapy for the treatment of GDM. Traditionally, insulin therapy has been the "gold standard" for the management of GDM, when diet therapy and exercise fail to achieve maternal glycemic control. Pregnant women have difficulty adhering to insulin therapy regimens because of the challenges with route of administration and schedule. Therefore, oral hypoglycemic agents such as glyburide and metformin are being increasingly used to treat GDM, and have been shown to have similar efficacy and safety as insulin, as well as lower cost and easier route of administration (Maymone et al., 2011; Nicholson & Baptiste-Roberts, 2011). The safety of insulin for use in pregnancy has been well established without the risk of transfer across the placenta. The FDA has not approved the use of glyburide or metformin for the treatment of women with GDM. This chapter will focus its discussion on glyburide.

3. Glyburide and its clinical pharmacokinetics

Glyburide is a second generation oral sulfonylurea, and its chemical structure is shown in Figure 1. Glyburide is indicated as an adjunct to diet therapy and serves to lower blood glucose levels in patients with type II diabetes mellitus (Feldman, 1985). Glyburide exerts its pharmacological effect by stimulating insulin secretion from pancreatic β-islet cells. It inhibits ATP-sensitive potassium channels on the surface of pancreatic β-islet cells, leading to cellular membrane depolarization. Depolarization at the cellular membrane prompts voltage-gated calcium channels to open, increasing the intracellular calcium concentration, which stimulates the release of insulin into the portal vein. Glyburide is administered in 1.25, 2.5 or 5 mg tablets. The FDA approved dosage range is 1.25 mg up to 20 mg per day. When higher dosages of glyburide are required, patients are typically switched to insulin.

Glyburide is a small lipophilic molecule (LogP = 4.8, MW = 494 Da) that is highly bound to plasma proteins (99.8% plasma protein binding). Glyburide is well absorbed with an oral bioavailability of approximately 95% for micronized tablets (Jonsson et al., 1994). It exhibits biphasic elimination kinetics with an initial distribution half-life ($T_{1/2\alpha}$) of roughly 30 min and a terminal elimination half-life ($T_{1/2\beta}$) of approximately 10 hours (Feldman, 1985; Jonsson et al., 1994). Thus, the overall elimination half-life of glyburide is approximately 4 hours. Glyburide has a small volume of distribution (0.2 L/kg), despite its lipophilic nature, and has negligible renal clearance.

Glyburide is extensively metabolized in the liver with a low hepatic extraction ratio. One enzyme involved in glyburide metabolism is CYP2C9, which is highly polymorphic. The CYP2C9 variant, CYP2C9*3, exhibits lower catalytic activity than wild-type CYP2C9*1 (Cavallari & Limdi, 2009). Kirchheriner et al. showed that the oral clearance of glyburide in the CYP2C9*3/*3 subjects (n = 3) was ~40% of that in CYP2C9*1/*1 subjects (n = 4) (Kirchheiner et al., 2002). Niemi et al. reported that the area under plasma concentration-time curve (plasma AUC) of glyburide in subjects heterozygous for CYP2C9*3 (CYP2C9*1/*3 or CYP2C9*2/*3, n = 2) was 280% of that in the CYP2C9*1/*1 subjects (n = 5) (Niemi et al., 2002). Yin et al. demonstrated that the oral plasma AUC of glyburide in CYP2C9*1/*3 subjects (n = 6) of the Chinese population was higher by ~100% as compared with that in the CYP2C9*1/*1 subjects (n = 12) (Yin et al., 2005). These clinical studies appear to suggest that CYP2C9 contributes significantly to glyburide metabolism *in vivo*.

On the other hand, *in vitro* studies using human liver microsomes have shown that CYP3A4 contributes greater than 50% of glyburide metabolism, while CYP2C9 contributes a much smaller percentage (Naritomi et al., 2004; Zharikova et al., 2009; Zhou et al., 2010a). Additionally, Lilja et al. showed that oral administration of clarithromycin, an inhibitor of CYP3A but not CYP2C9, significantly increased C_{max} and the plasma AUC of glyburide (Lilja et al., 2007). The epidemiological study (Schelleman et al., 2010) and case reports (Bussing & Gende, 2002; Leiba et al., 2004) all indicated that the concomitant use of glyburide with clarithromycin was associated with severe hypoglycemia. Thus, CYP3A also appears to contribute to glyburide metabolism *in vivo*. It is possible that glyburide is metabolized *in vivo* through the joint actions of hepatic CYP3A and CYP2C9.

In vitro metabolism studies using human liver microsomes or recombinant systems revealed that, besides CYP3A4 and CYP2C9, glyburide was also metabolized by other cytochrome P450 enzymes such as CYP3A5, CYP2C8 and CYP2C19, but to a much lesser extent (Naritomi et al., 2004; Zharikova et al., 2009; Zhou et al., 2010a). Zharikova et al. determined five metabolites of glyburide formed in human liver microsomes: M1 (4-*trans*-hydrocyclohexyl glyburide), M2a (4-*cis*-hydrocyclohexyl glyburide), M2b (3-*cis*-hydrocyclohexyl glyburide), M3 (3-*trans*-hydrocyclohexyl glyburide), M4 (2-*trans*-hydrocyclohexyl glyburide) and M5 (ethylene-hydroxylated glyburide) (Zharikova et al., 2009; Zharikova et al., 2007). The chemical structures of these glyburide metabolites are shown in Figure 1. CYP3A4 catalyzes the formation of M1-M5. CYP2C9 catalyzes the formation of M1-M3. CYP2C8 catalyzes the formation of M1, M2b, M3 and M4. CYP2C19 catalyzes the formation of M2a, M2b and M3 (Zharikova et al., 2009; Zharikova et al., 2007). The two major metabolites of glyburide, M1 and M2b, which account for approximately half of all the metabolites formed *in vitro* by human liver microsomes (Zharikova et al., 2007), are excreted into the bile and urine (~50% each) (Feldman, 1985). M1 and M2b are not likely to contribute significantly to hypoglycemic action in humans since they are only weakly active ($1/400^{th}$ and $1/40^{th}$ as active, respectively, as glyburide in preclinical models, as described in the FDA labeling). However, there were also studies indicating that M1 and M2b retain 75% and 50%, respectively, of the hypoglycemic activity of glyburide in humans (Rydberg et al., 1994). The systemic exposure of M1 is only 2 – 4% of that of glyburide (Zheng et al., 2009). The pharmacological activity of other glyburide metabolites is currently not known.

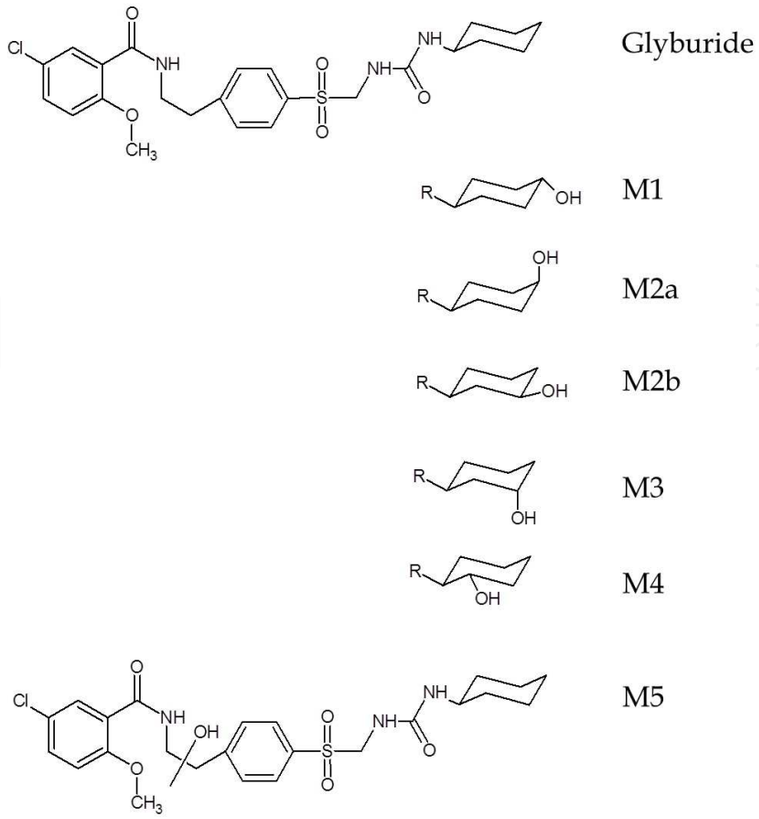

Fig. 1. The chemical structures of glyburide and its metabolites. M1, 4-*trans*-hydrocyclohexyl glyburide; M2a, 4-*cis*-hydrocyclohexyl glyburide; M2b, 3-*cis*-hydrocyclohexyl glyburide; M3, 3-*trans*-hydrocyclohexyl glyburide; M4, 2-*trans*-hydrocyclohexyl glyburide; and M5, ethylene-hydroxylated glyburide.

4. The efficacy and safety of glyburide during pregnancy

Although glyburide is not currently approved by the FDA to treat GDM, the pathophysiology of GDM is similar to type II diabetes mellitus and consequently, glyburide has been increasingly prescribed to women with GDM. There are obvious benefits to using oral hypoglycemic agents such as glyburide and metformin rather than insulin. Oral agents are less expensive, easier to administer and demonstrate improved patient compliance as compared to insulin. Clinical studies have been conducted to compare the efficacy and safety of such oral agents with those of insulin for the treatment of GDM. In this section, the results of clinical studies comparing the efficacy and safety of glyburide versus insulin will be summarized.

4.1 Clinical efficacy during pregnancy

There are several randomized controlled clinical trials that examined the efficacy of glyburide during pregnancy (Langer et al., 2000; Anjalakshi et al., 2007; Bertini et al., 2005; Ogunyemi et al., 2007). Langer et al. performed the largest clinical study that compared the efficacy of glyburide to insulin for the treatment of GDM (Langer et al., 2000). This group randomly assigned 404 women with GDM into two treatment groups (insulin or glyburide),

and showed no statistically significant difference in fasting, preprandial, 2-hour postprandial and mean blood glucose concentrations between the glyburide and insulin groups (~106 mg/dL, 105 mg/dL, 130 mg/dL, and 115 mg/dL, respectively). Langer concluded that glyburide was as effective as insulin for the treatment of GDM and therefore can be used as a clinically effective alternative to insulin therapy. These authors reported eight women in the glyburide group (4%) who required insulin therapy. These authors also performed a subsequent analysis of the data from this clinical study to determine if the severity of GDM was linked to the dosage of glyburide required to achieve adequate glycemic control (Langer et al., 2000). It was found that glyburide doses were increased and the success rate of glyburide therapy decreased as disease severity increased. At each level of disease severity, there was no difference in maternal and neonatal outcomes between the insulin and glyburide groups.

Two smaller clinical studies also compared the efficacy of glyburide and insulin in the treatment of GDM, and no difference was observed in fasting and 2-hour postprandial blood glucose concentrations (Anjalakshi et al., 2007; Bertini et al., 2005). In contrast, Ogunyemi et al. reported significantly higher fasting and 2-hour postprandial blood glucose concentrations in patients receiving glyburide than in patients receiving insulin (Ogunyemi et al., 2007). Bertini et al. found that glucose control was not achieved in 5 patients in the glyburide group (20.8% failure rate) who had to switch to insulin therapy, despite similarities in maternal demographics across groups (age, weight and parity) (Bertini et al., 2005). Since the sample size of this randomized-controlled trial was relatively small, this may not accurately reflect the true failure rate of glyburide therapy.

In addition, retrospective studies have been conducted to assess the efficacy of glyburide. Jacobson et al. performed a retrospective study of 584 women with GDM who had failed diet therapy and were treated with glyburide or insulin between the years of 1999-2002 (Jacobson et al., 2005). Patients from both groups were similar in age and nulliparity; however, women in the insulin group weighed more on average and had a higher mean fasting blood glucose level (105.4 versus 102.4 mg/dL). Women in the glyburide group had significantly lower post-treatment fasting and postprandial blood glucose levels. The failure rate of glyburide was reported to be 12%. The glyburide group did experience a higher rate of preeclampsia (12% versus 6%), despite controlling for body mass index and ethnicity. Jacobson et al. observed no statistical difference in neonatal outcomes such as birth weight and macrosomia, as well as incidence of cesarean delivery between groups. Ramos et al. retrospectively examined the effectiveness of glyburide (n = 44) versus insulin (n = 78) in women with GDM who had a 50 g 3-hour oral glucose challenge test of ≥200 mg/dL and a pretreatment fasting plasma glucose level of ≥105 mg/dL (Ramos et al., 2007). There were no significant differences between the two groups with respect to blood glucose levels. The failure rate of glyburide was 16%. There were no significant differences in fetal outcomes between the two treatment groups; however, the incidence of neonatal hypoglycemia was higher in glyburide-treated women (34% versus 15%, respectively) (Ramos et al., 2007). It is worth noting that retrospective studies were often not adequately powered and were without adequate controls. Therefore, making general conclusions regarding the efficacy of glyburide is difficult.

To predict the treatment failure rate for glyburide in women with GDM, Kahn et al. conducted a prospective cohort study (n = 75) which demonstrated that fasting blood glucose levels ≥ 110 mg/dL, in women with GDM, were associated with higher glyburide

failure rates (Kahn et al., 2006). The authors also reported that women who were older, had more than one child and were diagnosed with GDM earlier in their pregnancy were more likely to fail glyburide therapy. On the other hand, Rochon et al. suggested that only higher mean blood glucose levels (≥ 200 mg/dL in the 50 g 1-hour oral glucose challenge test) were indicators of glyburide failure (Rochon et al., 2006).

4.2 Maternal and neonatal safety

Several studies have been conducted to investigate the adverse effects of glyburide versus insulin (Anjalakshi et al., 2007; Bertini et al., 2005; Langer et al., 2000; Ogunyemi et al., 2007; Yogev et al., 2004). Among these studies, Langer et al. conducted the largest randomized controlled trial with 404 pregnant women to receive glyburide or insulin, and found a significantly higher percentage of women with a blood glucose level <40 mg/dL in the insulin group compared with the glyburide group (20% versus 4%) (Langer et al., 2000). Yogev et al. demonstrated that 19 of 30 insulin-treated patients with GDM (63%) experienced asymptomatic hypoglycemia versus 7 of 25 (28%) glyburide-treated patients (Yogev et al., 2004). On the other hand, in the study with 97 pregnant women, Ogunyemi et al. did not report a significant difference in hypoglycemia between the insulin and glyburide groups (31% verse 38%, respectively) (Ogunyemi et al., 2007). Other studies reported no hypoglycemic events (Anjalakshi et al., 2007; Bertini et al., 2005). Although the results varied, possibly due to difference in definition of hypoglycemia, these studies appear to support the notion that glyburide therapy generally causes fewer hypoglycemic events than insulin therapy. Langer et al. also showed no difference in the incidence of preeclampsia among women treated with insulin or glyburide (Langer et al., 2000). Bertini et al. found no significant difference in changes in maternal weight of women treated with insulin as compared to glyburide (Bertini et al., 2005). Likewise, no significant differences were reported in the percentage of women with cesarean delivery in the insulin group compared with the glyburide group (Anjalakshi et al., 2007; Bertini et al., 2005; Langer et al., 2000; Ogunyemi et al., 2007).

Various clinical studies have also analyzed the effects of glyburide and insulin on neonatal adverse outcomes. In an earlier study, Coetzee and Jackson treated over 600 pregnant women suffering from GDM or type II diabetes mellitus with glyburide/metformin combination therapy (Coetzee and Jackson, 1985). Patients were classified as new diabetics, known diabetics or untreated diabetics. The untreated diabetic group was made up of pregnant women with type II diabetes mellitus or GDM who were not seen in the clinic until term. Each class of patients was further organized into four treatment groups: (1) diet therapy, (2) diet plus metformin therapy, (3) diet plus glyburide therapy, (4) diet plus metformin/glyburide combination therapy, and (5) treatment group (4) with the addition of insulin therapy due to inadequate glucose control (Coetzee and Jackson, 1985). Metformin therapy appeared to be the safest (0 still births, 1 neonatal death, and 33 per 1,000 perinatal morbidities, i.e. large for gestational age, low birthweight, hypoglycemia, jaundice and congenital abnormalities), followed by glyburide (1 still birth, 0 neonatal deaths, and 43 per 1,000 perinatal morbidities) and the emergency insulin group (1 still birth, 4 neonatal deaths, and 59 per 1,000 perinatal morbidities). In women with newly diagnosed GDM, insulin therapy appeared to be the safest (no adverse birth outcomes), followed by metformin (1 neonatal death and 16 per 1,000 perinatal morbidities) and glyburide (1 still birth and 42 per 1,000 perinatal morbidities). The authors also reported a decrease in perinatal morbidities among the glyburide group compared with the diet therapy group as well as zero cases of serious neonatal hypoglycemia.

Bertini et al. found just the opposite to be true in a clinical study with 70 patients diagnosed with GDM (Bertini et al., 2005). Patients were placed on insulin therapy (n = 27), glyburide therapy (n = 24) or acarbose therapy (n = 19). The authors reported that neonatal hypoglycemia was observed in 8 newborns, 6 of which were from the glyburide group. Likewise, in the study with 97 women (n = 49 in the insulin group and n = 48 in the glyburide group), Ogunyemi et al. reported that 28% of infants in the glyburide group experienced an episode of hypoglycemia versus 13% in the insulin group, and the difference was statistically significant (Ogunyemi et al., 2007). In contrast, Langer et al. showed no difference in the incidence rate of hypoglycemia for infants between the insulin and glyburide treatment groups (Langer et al., 2000). Bertini et al. also demonstrated that a significantly higher percentage of fetuses were large for gestational age (LGA) infants in the glyburide group compared with the insulin group (25% versus 3.7%, respectively) (Bertini et al., 2005); however, Langer et al. reported comparable incidence rates of LGA between the two groups (n = 404) (Langer et al., 2000). All the clinical studies consistently reported higher average infant birth weights in the glyburide group than the insulin group, but the difference was small (an average of ~100 g) and not statistically significant (Anjalakshi et al., 2007; Bertini et al., 2005; Langer et al., 2000; Ogunyemi et al., 2007). Few congenital malformations or anomalies were reported in either group. It is worth noting that the study by Langer et al. investigated significantly more subjects than any other study, and hence the results obtained could be more adequately powered and reliable.

Overall, in women with GDM, glyburide achieved similar efficacy of glycemic control as insulin therapy. The maternal and neonatal safety of glyburide does not substantially differ from insulin therapy. However, it should be noted that, at present, there is no long-term safety data for infants whose mothers were treated with glyburide. Thus, further studies are needed to assess the long-term effects of maternal glyburide administration on child and adolescent development (neurologic and behavioral) as well as the incidence rate of type II diabetes mellitus and obesity.

5. Pregnancy-induced pharmacokinetic changes of glyburide

Physiological and biochemical changes that occur in pregnancy may affect the pharmacokinetics of drugs, namely absorption, distribution, metabolism and elimination (Anderson, 2005; Klieger et al., 2009; Loebstein et al., 1997). Such changes include, among others, changes in volume of distribution of drugs and plasma protein binding (Loebstein et al., 1997; Mendenhall, 1970), induction or down-regulation of cytochrome P450 enzyme expression and activity (Hebert et al., 2008; Tracy et al., 2005), and increase in renal blood flow and glomerular filtration (Dunlop & Davison, 1987). The effects of such pregnancy-induced pharmacokinetic changes may be such that a dosage adjustment is required to accommodate increased potency of a drug or decreased efficacy. However, the balance of treating the mother and protecting the fetus may likely present challenges specifically for drug compounds that require increased dosages in order to be effective during pregnancy. Glyburide is such a case.

5.1 Clinical pharmacokinetic studies

To evaluate pregnancy-induced changes in the pharmacokinetics of glyburide, Hebert et al. compared parameter estimates for steady-state pharmacokinetics of glyburide in pregnant women with GDM (n = 40) and non-pregnant women with type II diabetes mellitus (n = 26)

(Hebert et al., 2009). Dose-normalized steady-state plasma concentrations of glyburide were approximately one-half in pregnant women with GDM as compared with those in non-pregnant women with type II diabetes mellitus, consistent with a 2-fold increase in apparent oral clearance of glyburide during pregnancy. Modeling and simulations of this data demonstrate that pregnant women with GDM require much higher dosages of glyburide to achieve comparable concentrations as non-pregnant women. Whether higher dosages will be required during pregnancy to achieve glycemic control still needs further study.

5.2 *In vivo* animal studies

In vivo pharmacokinetic studies in pregnant mice have been performed to investigate the mechanism of pregnancy-induced increase in the apparent oral clearance of glyburide (Zhou et al., 2010b). Several groups have shown that CYP3A is a major enzyme responsible for the *in vitro* metabolism of glyburide (Naritomi et al., 2004; Zharikova et al., 2009; Zhou et al., 2010a). It has also been well established that hepatic CYP3A activity is significantly induced by pregnancy (Hebert et al., 2008; Tracy et al., 2005). Therefore, it has been hypothesized that pregnancy induces the activity of hepatic CYP3A, resulting in an increase in the oral clearance of glyburide (Zhou et al., 2010b). Since it has been shown that the levels of hepatic Cyp3a content in pregnant mice and its activity measured using testosterone as the probe substrate are significantly increased compared with those in non-pregnant mouse controls (Mathias et al., 2006; Zhang et al., 2008), the pregnant mouse was used as the animal model to test this hypothesis (Zhou et al., 2010b). Upon characterization, the pharmacokinetics of glyburide indeed demonstrated a two-fold increase in its hepatic clearance in pregnant mice on gestation day 15 compared to non-pregnant mice, a magnitude of change similar to that observed in the human clinical study, but with no changes in plasma protein binding (Zhou et al., 2010b).

To investigate the mechanism of this pharmacokinetic change in pregnant mice, Zhou et al. further determined glyburide depletion in mouse hepatic S-9 fractions and found the half-life of glyburide depletion to be markedly shorter in S-9 fractions from pregnant mice compared to non-pregnant mice. Glyburide depletion was also inhibited to a large extent by the Cyp3a inhibitor, ketoconazole, suggesting that the increase in hepatic clearance of glyburide during pregnancy may be due to an increase in the activity of hepatic Cyp3a (Zhou et al., 2010b). These studies support the notion that CYP3A plays a significant role in the clearance of glyburide in pregnancy. This finding has significant clinical implications. For example, significant drug-drug interactions may occur with glyburide and CYP3A inducers or inhibitors (Lilja et al., 2007).

5.3 Placental transport of glyburide

Hebert et al. have also shown that glyburide concentrations are measurable in umbilical cord blood at the time of delivery, suggesting that glyburide crosses the placenta and thus may pose adverse effects on the developing fetus (Hebert et al., 2009). The average umbilical cord to maternal plasma concentration ratio of glyburide was 0.7 ± 0.4 (Hebert et al., 2009). This less than unity ratio indicates that glyburide does not cross the placental barrier entirely by passive diffusion, even though it is highly lipophilic (LogP = 4.8). Many ATP-binding cassette (ABC) efflux transporters such as P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and multidrug resistance proteins (MRPs) are highly expressed on the apical membrane of placental syncytiotrophoblasts facing maternal blood, where they

protect the fetus by expelling drugs, xenobiotics, and metabolites from the fetal compartment to the maternal circulation (Behravan & Piquette-Miller, 2007; Ceckova-Novotna et al., 2006; Mao, 2008; Ni & Mao, 2010). Glyburide has been shown to be a substrate of such ABC efflux transporters. Thus, it is likely that ABC efflux transporters in the placenta play an important role in limiting fetal exposure to glyburide.

To test this hypothesis, Gedeon et al. examined the role of P-gp, BCRP and MRPs in the efflux of glyburide using stable cell lines expressing these transporters in the presence or absence of selective inhibitors (Gedeon et al., 2006). Their results suggested that glyburide was preferentially transported by BCRP and MRP3, but not by P-gp, MRP1 or MRP2. Likewise, Gedeon et al. demonstrated that inhibition of P-gp or MRP1 did not affect accumulation of [^{3}H]-glyburide in inside-out brush border human placental membrane vesicles; however, inhibition of BCRP did (Gedeon et al., 2008b). Using the dually perfused human placental cotyledon model, Gedeon et al. further showed that the rate of transfer of glyburide across the placenta in the presence of indomethacin (an inhibitor of MRP1, MRP2 or MRP3) was not different from the rate of transfer in the absence of inhibitor (Gedeon et al., 2008a), suggesting that MRP1, 2, or 3 may be only minimally involved in the transport of glyburide across the human placenta. On the other hand, the role of BCRP in the transfer of glyburide across the human placenta was confirmed in a similar human placental perfusion study (Pollex et al., 2008). In contrast, Hemauer et al showed that MRP1 appears to play a greater role in the efflux of glyburide than P-gp or BCRP (Hemauer et al., 2010). Using inside-out brush border membrane vesicles isolated from human term placentas in the presence or absence of selective inhibitors (verapamil for P-gp, Ko143 for BCRP, and indomethacin for MRP1), Hemauer et al. determined the relative contribution of P-gp, BCRP, and MRP1 to the uptake of glyburide into the inside-out membrane vesicles to be 9 ± 5%, 25 ± 5%, and 43 ± 4%, respectively (Hemauer et al., 2010).

Zhou et al. confirmed that glyburide is a substrate for human BCRP and mouse Bcrp1 using Madin Darby canine kidney (MDCK) cell transwell transport experiments (Zhou et al., 2008). Zhou et al. also characterized glyburide disposition in wild-type and Bcrp1$^{-/-}$ pregnant mice to elucidate the role of Bcrp1 in limiting glyburide transfer across the placenta to the fetal compartment. The results showed that the maternal plasma concentration-time profiles remained the same between wild-type and knockout mice; however, the fetal area under the concentration-time curve (AUC) of glyburide in Bcrp1$^{-/-}$ pregnant mice was two times greater than that in wild-type mice (Zhou et al., 2008). It is worth noting that the amount of glyburide entering the fetus only accounts for a small fraction of the total amount of glyburide in the body (Zhou et al., 2008). These results confirm that BCRP and Bcrp1 are important determinants of fetal exposure to glyburide (Zhou et al., 2008). All these *in vitro*, *ex vivo*, and *in vivo* studies suggest that ABC efflux transporters, particularly BCRP, are important in protecting the fetus from exposure to glyburide. Thus, if a drug known to be a BCRP inhibitor is co-administered with glyburide, fetal exposure to glyburide may be increased through inhibition of placental BCRP.

5.4 Placental metabolism of glyburide

The placenta may also protect the fetus by metabolizing drugs or xenobiotics ingested by the mother. Human term placentas have been used in several studies to characterize placental metabolism of glyburide (Jain et al., 2008; Zharikova et al., 2009; Zharikova et al., 2007). Zharikova et al. reported that placental microsomes converted ~87% of glyburide to the M5

metabolite (ethylene-hydroxylated glyburide), and the rest to other metabolites (Zharikova et al., 2007). When compared to human liver microsomes; however, the total V_{max} for all metabolites was much lower for placental microsomes (13 ± 0.8 pmol/min/mg protein) than human liver microsomes (213 ± 37 pmol/min/mg protein). Although the relative contribution of placental drug-metabolizing enzymes to the overall disposition of glyburide may in fact be minimal, the formation of M5 in such close proximity to the fetus could have clinical implications for fetal metabolite exposure. However, at this time, the pharmacological activity of M5 is unknown. Zharikova et al. further identified CYP19 to be the major drug-metabolizing enzyme responsible for the biotransformation of glyburide to M5 in the human placenta (Zharikova et al., 2009). The intrinsic clearance of CYP19 for glyburide was 0.02 μL/min/pmol CYP and only represented 1.8% of the overall intrinsic clearance of human liver microsomes for glyburide.

Jain et al. studied glyburide metabolism using placental microsomes isolated from human term placentas from women with uncomplicated pregnancies, women with GDM on diet therapy, or women with GDM on glyburide (Jain et al., 2008). They found that placental microsomes from uncomplicated pregnancies showed higher M1 and M2 metabolite formation rates compared to placentas from women with GDM on diet therapy or on diet therapy plus glyburide. However, there was no difference in glyburide metabolism between placentas from diet therapy and diet therapy plus glyburide (Jain et al., 2008). The differences in placental microsomal metabolite formation may reflect the effects of GDM on the placenta. Histologic abnormalities in the placenta are more common in women with GDM than non-diabetic controls (Daskalakis et al., 2008).

Based upon the results obtained so far, the placenta appears to play a very minor role in determining maternal disposition of glyburide, but may play a significant role in controlling fetal exposure to the drug and metabolites. Very limited data is available in this regard, and the role of placental metabolism in controlling fetal drug exposure warrants further investigation.

6. Conclusions

Although insulin therapy has been the "gold standard" for the treatment of GDM, the increasing use of oral anti-diabetic agents such as glyburide and metformin has begun to change the standard of care. Glyburide is a second generation sulfonylurea. Clinical studies demonstrate that glyburide is a safe alternative to insulin therapy for the treatment of GDM due to its similar efficacy to insulin, relatively low fetal exposure, lower cost and ease of administration. The pharmacokinetic properties of glyburide resulting in low fetal exposure include: high plasma protein binding, a relatively short elimination half-life, and efflux transport by ABC transporters such as BCRP in the placenta. Glyburide is also metabolized in the placenta by CYP19, which may limit fetal exposure to the parent compound but simultaneously expose the fetus to metabolites. However, it is reassuring that the currently used glyburide dosage range for pregnant women with GDM has comparable maternal, fetal and neonatal outcomes as insulin therapy.

In addition to the concern of fetal exposure, physiological changes that occur during pregnancy may alter the pharmacokinetics of glyburide, thus affecting the safety and efficacy of the drug for both the mother and the fetus. Indeed, a recent clinical study has demonstrated that the apparent oral clearance of glyburide is increased two-fold in

pregnant women with gestational diabetes as compared to non-pregnant women with type II diabetes mellitus (Hebert et al., 2009). This finding implies the need for further evaluation and dosage optimization for glyburide during pregnancy. The mechanism of such a change in glyburide disposition during pregnancy has not been fully understood, but is likely related to increased expression and activity of cytochrome P450 enzymes in the liver, such as CYP2C9 and CYP3A.

In summary, glyburide has been increasingly used for the treatment of GDM with similar safety and efficacy to insulin therapy. The mechanistic understanding of pregnancy-induced changes in the disposition of this drug (including fetal exposure) will be important for optimizing dosage guidelines for glyburide during pregnancy.

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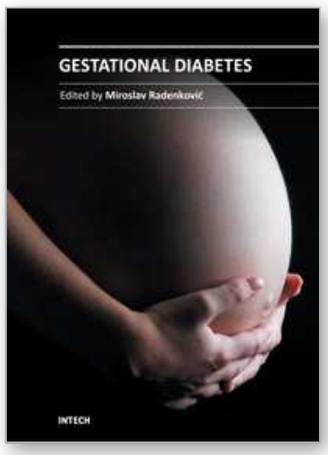

Gestational Diabetes

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Gestational diabetes mellitus is defined as hyperglycemia with onset or first recognition during pregnancy. The incidence of gestational diabetes is still increasing and this pathological condition has strong association with adverse pregnancy outcomes. Since gestational diabetes can have long-term pathological consequences for both mother and the child, it is important that it is promptly recognized and adequately managed. Treatment of gestational diabetes is aimed to maintain euglycemia and it should involve regular glucose monitoring, dietary modifications, life style changes, appropriate physical activity, and when necessary, pharmacotherapy. Adequate glycemic control throughout the pregnancy can notably reduce the occurrence of specific adverse perinatal and maternal outcomes. In a long-term prospect, in order to prevent development of diabetes later in life, as well to avoid associated complications, an adequate education on lifestyle modifications should start in pregnancy and continue postpartum.

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